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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

CELSA, BENNETT M

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 08/11/2003

4

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.
09/904,117

Applicant(s)
Muir et al.

Examiner
Bennett Celsa

Art Unit
1639



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Status of the Claims

Claims 1-11 are currently pending and under consideration.

Specification

1. Applicant's computer readable form (CRF) and corresponding paper sequence listing has been received and entered. However, the disclosure is objected to because of the following informalities: the specification must be amended to insert the sequence identifiers, where appropriate, in order to satisfy the sequence rules.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Priority

3. With respect to claims 1, 4, 6 and 8-10 which recite new matter (e.g. "conjugated thiol") Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional

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application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). Accordingly, these claims are afforded the filing date of the present application (e.g. 7/12/01) for purposes of prior art.

Specification

4. Claims 1, 4, 6 and 8-10 are objected to because of the following informalities: The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. Claim 1 (and claims dependent thereon) recite “conjugated thiol” which lacks specification antecedent basis. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1 (and claims dependent thereon) the use of the term “conjugated thiophenol” is confusing as to the encompassed structure. It is noted that this term is not defined in the

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specification and is confusing as to how or if a “conjugated” “thiophenol” differs from “thiophenol”? How does the term “conjugated” chemically modify (if at all) thiophenol?

B. In claim 2, the recited members of the Markush of “conjugated thiophenols” is improper, since it is not chemically understood how a “conjugated thiophenol” can encompass benzoic and pyridine compounds present in the Markush groups.

C. In claim 1 (and claims dependent thereon), the phrase “said bound recombinant protein” lacks antecedent basis.

D. Claim 1 (and dependent claims thereof) are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are failure to recite that the ligation of the peptide and protein occur “end to end” as a result of the “spontaneous intramolecular rearrangement of an N-terminal cysteine of the peptide with the C-terminal thioester of the protein e.g. the process is chemoselective; and failure to include a step effecting the “said bound recombinant protein”.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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8. Claims 1, 4, 6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (lack of written description).

The present claims are directed to a method of cleaving a recombinantly expressed protein for generating a protein intermediate for ligation to a peptide containing an N-terminal cysteine which employs the use of “a conjugated thiol”. However, the term “conjugated thiol” lacks metes and bounds regarding what structure is encompassed by this terminology since

- I. this term (“conjugated thiol”) is not defined in the specification and
- ii. It is confusing as to how or if a “conjugated” “thiol” differs from “thiophenol”? How does the term “conjugated” chemically modify (if at all) thiophenol

The specification description (e.g. see Markush of claim 2) is directed to specific thiophenol compounds containing unsubstituted and specifically substituted thiophenols as well as compounds which lack thiophenol core structure (e.g. 2 thiopyridine) which clearly does not provide an adequate representation regarding the open ended claimed “conjugated thiophenol” compounds which encompass any derivative of a thiophenol core structure.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject matter

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sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the scope of thiophenol derivatives . In this regard, it is noted that thiophenol core structure appears to be critical regarding the successful practice of the presently claimed invention as admitted in the specification (e.g. “Surprisingly, thiophenol, was found to be the only co-factor tested that supports both efficient cleavage and efficient ligation”: see specification page 24, especially lines 20-23). Additionally, the narrow scope of exemplified unsubstituted and substituted thiophenols are clearly not representative of the scope of the presently claimed “conjugated thiophenol” compounds.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 4, 6, 8 and 10 are rejected under 35 U.S.C. 102(a,b) as being anticipated by Severinov et al. J. Biol. Chem. Vol. 273, (June 1998) pages 16205-16209.

Severinov et al. teach "expressed protein ligation" which comprises expressing a protein in a procarye (E.Coli) utilizing a vector (pCYB) in which the protein is bound to an intein-chitin binding domain (CBD) and the subsequent ligation (in situ, e.g. in a single pot) to a peptide containing an N-terminal cysteine having an unoxidized sulfhydryl side chain in the presence of a "conjugated thiol" (e.g. thiophenol), buffer at pH @7 to effect cleavage of the protein-CBD to form a C-terminal protein thioester which forms a covalent bond to the peptide following an intramolecular rearrangement See abstract and entire article.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 4, 6, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier) and Dawson Science Vol. 266 (11/4/94) pages 776-779.

Comb et al. teach a method of expressing a protein in both procaryotic (E.Coli) and eucaryotic (yeast) in which the protein is bound to an intein-chitin binding domain (CBD) and subsequently ligated (in situ, e.g. in a single pot) to a peptide containing an N-terminal cysteine having an unoxidized sulfhydryl side chain in the presence of a thiol, buffer at pH @7 to effect cleavage of the protein-CBD to form a C-terminal protein thioester which forms a covalent bond to the peptide following an intramolecular rearrangement. See. E.g. Comb et al. at col. 7-8; Figure 28 (reaction scheme); Examples (especially examples 15 and 19; Patent claims (especially claims 96-103).

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The Comb et al. reference differs from the presently claimed method by failing to explicitly teach the incorporation of a "conjugated thiol" to promote ligation.

However, Comb et al. specifically teaches the use of the Dawson native chemical ligation technique (e.g. see Comb at col. 75, lines 50-60) as outlined in Dawson et al. Science Vol. 266: 776-779 (1994) in which Dawson employs the use of "benzyl mercaptan" (e.g. a "conjugated thiol" wherein benzyl is conjugated and mercaptan corresponds to thiol) in pH@7 in buffer to effect chemical ligation. See Dawson (1994) page 778, Fig. 3 and footnote 30 on page 779 teaching benzyl mercaptan).

Accordingly, the Comb et al. Reference incorporation of the Dawson native chemical ligation technique which employs a "conjugated thiol" would provide motivation to one of ordinary skill in the art to employ a conjugated thiol in the Comb ligation scheme.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize a "conjugated thiol" (e.g. benzyl mercaptan) in the Comb et al. process as suggested by Dawson (1994).

13. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier) and Dawson Science Vol. 266 (11/4/94) pages 776-779 as applied to claims 1, 4, 6, 8 and 9 above, and further in view of Kent WO 96/34878 and/or Dawson et al. JACS Vol. 119, No. 19 (5/97).

The teaching of the Comb et al. And Dawson (Science) reference recited above is hereby incorporated by reference in their entirety.

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The Comb et al. and Dawson(Science) reference teachings differ from the presently claimed invention by failing to explicitly teach the use of “conjugated thiols” including thiophenol in the Comb method of ligating a recombinantly produced intein protein with a peptide having an N-terminal cysteine residue.

The Kent WO 96/34878 reference teaches the advantages of using “conjugated thiols” (including thiophenol) in a method of synthesizing peptides/proteins using “native chemical ligation” (e.g. the Dawson Science method) including keeping the cysteine side chains reduced. Eg. See Kent WO 96/34878 at pages 7, 14 , examples and claims 1-7.

Similarly, the Dawson (JACS) reference teaches the advantages of using thiol additives (e.g. thiophenol) in “native chemical ligation” including “keeping the cysteine chain reduced”, “catalyzing the reversal of unproductive thioester formation and “generating a more reactive phenyl thioester” (e.g see abstract). Both the Dawson (JACS) and Kent WO 96/34878 references perform chemical ligation using buffers and pH @7.

Accordingly, the Dawson (JACS) and/or Kent WO 96/34878 references would provide motivation to one of ordinary skill in the art to employ a conjugated thiol (e.g. thiophenol) in the Comb ligation scheme.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant’s invention to utilize a “conjugated thiol” (e.g. thiophenol) in the Comb et al. process as suggested by both the Dawson (JACS) and Kent WO 96/34878 references

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14. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier), Dawson(Science), Dawson (JACS) and Kent WO 96/34878 references as applied to claims 1-9 above, and further in view of Chong et al. Gene (6/97) pages 271-281.

The separate and combined teachings of the Comb et al, Dawson (Science), Dawson (JACS) and Kent WO 96/34878 references recited above are hereby incorporated by reference in their entirety.

The Comb et al. Reference ligation method differs from the presently claimed invention (e.g. claims 10-11) in teaching the use of the vector pMYB in E.Coli. instead of the vector pCYB to make the recombinantly expressed protein.

However, the Chong et al. Reference teaches the interchangeable use of the pMYB and pCYB vectors in the recombinant making of chitin-binding domain (CBD) (e.g. recombinant heterologous proteins) in E.Coli containing intein constructs which undergo a self-cleavage reaction at its N-terminal peptide linkage in the same manner as utilized by the Comb et al. reference prior to instituting chemical ligation with an N-terminal cysteine containing peptide/protein. In this regard, the Chong et al. reference explicitly teaches the utilization of the resulting thiol esters as intermediates in peptide ligation (citing Dawson et al. 1994) and pCYB as a "commonly used expression vector" for expressing heterologous proteins in E. Coli. .E.g. see Chong et al. Abstract; Fig. 1 (a), examples utilizing pCYB vectors and page 279

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Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the pCYB vector to make the recombinantly expressed protein in the Comb et al. ligation method since this vector is taught to be functionally equivalent to the pMYB vector e.g. as used in E.Coli to recombinantly synthesize a protein bound to an intein-chitin binding domain.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 09/879,744. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed method is a species (e.g. simultaneous cleavage; conjugated thiophenol) of the present application which is drawn to generically cleaving and conjugated thiols.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)
August 8, 2003

BENNETT CELSA
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to be 'Bennett Celsa', written over the printed name and title.